REMARKS

This document is filed in reply to the Office Action dated March 14, 2005 ("Office Action"). Applicants also file herewith an Information Disclosure Statement.

At the Examiner's request, Applicants have replaced Figures 1-7, 13, and 14 with amended versions that include SEQ ID NOs. The specification is amended to correct an informality. Applicants also amend claim 1 to delete parts (b)-(d) and add new claims 20-31. Claim 2 is amended to promote clarity.

Support for the limitation "wherein the protein binds to a hematopoietin factor" recited in new claim 24 appears at page 8, line 11 of the specification. Support for new claims 20-31 can be found in original claim 1, 3, 5, 7, and 11 and the specification. Examples of the support are listed in Table 1 below. No new matter has been introduced.

Table 1. Support for New Claims

New Claims	Support in
Claim 20	part (b) in original claim 1
Claim 24	part (c) in original claim 1
Claims 21 and 25	original claim 3
Claims 22 and 26	original claim 5
Claims 23 and 27	original claim 7
Claims 28 and 30	original claim 11
Claims 29 and 31	original claim 12

Upon entry of the proposed amendments, claims 1-31 will be pending. Claims 9-19 have been withdrawn from further consideration as drawn to non-elected inventions. Applicants intend to request rejoinder of method claims 11, 12, and 28-31 once the present composition claims are deemed allowable. Claims 1-8 and 20-27 are now under examination. Reconsideration of this application is requested in view of the following remarks.

Objections to the Specification

The Examiner objected to the specification for not complying with the sequence rules. See the Office Action, page 2, lines 8 and 9.

According to the Examiner, the sequences presented in Figures 1-7, 13, and 14 are not referred to by SEQ ID NOs in the "Description of Drawing" section of the specification. Applicants would like to point out that this section was already amended to include SEQ ID NOs that refer to the sequences. See the "Response To Notice To Comply With Requirements For Patent Applications Containing Nucleotide And/Or Amino Acid Sequences" filed on December 30, 2002. The Examiner also requested that SEQ ID NOs be recited in the figures. Applicants have amended the figures accordingly.

In view of the above remarks and amendments, Applicants submit that the objections should be withdrawn.

Rejection under 35 U.S.C. § 101

The Examiner rejected claims 1-8 for lack of utility on various grounds. See page 3, lines 1 and 2 of the Office Action. Applicants traverse each of the grounds below, discussing amended claim 1 first. This claim is drawn to an isolated nucleic acid containing a sequence that encodes a protein comprising the sequence of SEQ ID NO: 2, 4, or 17.

I

The Examiner asserted that "Applicant has not disclosed any specific and substantial utility ... for the claimed invention." See the Office Action, page 3, lines 3 and 4.

Applicants disagree. In fact, the specification discloses that the proteins of SEQ ID NOs: 2, 4, and 17 (NR10.1, NR10.2, and NR10.3, respectively) are hemopoietin receptor proteins. They bind to a hematopoietin factor. See, e.g., the specification, page 3, line 4; and page 8, line 8. Accordingly, they "can be applied for diagnosis and treatment of diseases related to immunity and hematopoiesis." See the specification, page 56, lines 27 and 28. Also, the specification discloses that a soluble extracellular domain of each protein can be used as an inhibitor "to suppress the cellular immunity or inhibit the proliferation of hematopoietic cells *in vivo* ... to suppresses the immune function or inflammation ... [or] to suppress the onset of autoimmune diseases arising from autoimmunity, or tissue rejection by the immune system of the living body, the primary problem in transplantation. Furthermore, the inhibitors may be effectively used to treat such diseases caused by the abnormally upregulated

immune response. Thus, it is possible to use the inhibitors to treat a variety of allergies ..." See the specification, page 57, last paragraph. Treatment of any of the above-mentioned disorders is without question a real-world, i.e., substantial, use. Likewise, each is a "specific" utility, in contrast with a "general" utility that would be applicable to the "broad class of the invention" (i.e., all proteins). The Revised Interim Utility Guidelines Training Materials at page 29 provide some hypothetical examples of utilities for proteins that do not qualify as "specific" utilities because they apply to "virtually every member of a very general class of materials, such as proteins ..." These examples include utility as a source of amino acids or as protein supplements for animal food. In contrast to such utilities that apply to all proteins, the presently asserted utilities clearly cannot be dismissed as "nonspecific."

The above asserted utilities are also credible. The invention of this application is based, at least in part, on the discovery of nucleic acids encoding proteins NR10.1, NR10.2, and NR10.3. Each of the proteins includes motifs that are conserved in well-known human cytokine receptors, such as gp130, leukemia inhibitory factor receptor, Oncostatin M receptor β subunit, IL-12 receptor β2 subunit, and NR6. See the specification, Fig. 2. Examples of the motifs include a WS motif, a YR motif, a proline-rich motif, and a box1 motif. These motifs are responsible for binding to a ligand or mediating signal transduction. See the specification, page 3, lines 20-27; page 4, lines 22-25; page 7, lines 16-21; and Fig. 2. In view of these teachings, one of ordinary skill in the art would recognize that the nucleic acid of claim 1 encodes a cytokine receptor that plays a role in immunity and hematopoiesis, as well as diseases related to those functions. In this connection, Applicants note that

> [T]the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

See MPEP 2107.02(VII). Here, a person of ordinary skill in the art to would conclude, based on the evidence in the specification coupled with what was known in the art, that the asserted utilities are more likely than not true. Therefore, it is submitted that the above asserted utilities are credible.

To further support credibility of the asserted utilities, Applicants submit three articles: Dillon et al., "Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice" Nature Immunology 5(7):752-760, July 2004; Diveu et al., "GPL, a Novel Cytokine Receptor Related to GP130 and Leukemia Inhibitory Factor Receptor" J. Biol. Chem. 278(50):49850-49859, December 12, 2003; and Kernebeck et al. "The signal transducer gp130: solution structure of the carboxy-terminal domain of the cytokine receptor homology region" Protein Science 8(1):5-12, 1999. Copies of these references are included in the Information Disclosure Statement filed herewith.

Dillon et al. says that Interleukin 31 (IL-31) signals through a receptor composed of IL-31 receptor A (IL-31 RA) and oncostatin M receptor. See the Abstract. IL-31 was identified via its binding to IL-31 RA variant 4 (IL-31RAV4), the sequence of which is identical to that of NR10.3 (SEQ ID NO: 17). See Dillon et al. page 753, right column, second paragraph. In other words, IL-31 is a ligand of NR10.3. The sequence of IL-31-RA and its alignment against SEQ ID NO: 17 are shown in Exhibits A and B, both attached hereto. Since NR10.3 and NR10.1 have the same extracellular domain and NR10.2 is a splice variant of NR10.1 that lacks transmembrane and intercellular domains but contains the same extracellular domain as NR10.1 and NR10.2, IL-31 is also a ligand of NR10.1 or NR10.2. Dillon et al. further describes transgenic mice that over-express IL-31, as well as non-transgenic mice to whom purified IL-31 was administered. The mice exhibited a phenotype that mimics inflammatory disease and allergy. See, e.g., page 755, right column, through page 757. The IL-31 was shown to be acting via IL-31-RA (page 757, columns 1-2, carryover paragraph).

Diveu et al. describes another IL-31 receptor A named GPL, the sequence of which (shown in Exhibit C) is substantially identical to NR10. According to Diveu et al., expression of GPL is induced by INFγ in monocytes and dendritic cells, suggesting that IL-31 and GPL are involved in inflammatory diseases. See page 49854, right column, lines 9-25.

Kernebeck et al. describes a family of cytokine receptors and domains conserved among its members, including the above-mentioned WS motif.

These three articles support the assertion that NR10.1, NR10.2, and NR10.3 are receptors of cytokines, e.g., IL-31, and are involved in immune system-related disorders, such as allergies and other inflammatory diseases. Accordingly, the receptors and nucleic acids encoding them can be used in isolating the cognate ligand (IL-31) or in treating inflammatory diseases, such as allergies, exactly as stated in the specification. In sum, they have credible utilities.

II

The Examiner asserted that "Applicant has not disclosed any ... well-established utility for the claimed invention." See the Office Action, page 3, lines 3 and 4.

Applicants first point out that a "well-established utility" by definition need not be "disclosed" by an applicant, as such a disclosure would mean it is an "asserted" rather than "well-established" utility. As set forth in MPEP 2107,

> An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

As discussed above, the nucleic acids of claim 1, encode hemopoietin factor receptor proteins. It is well known in the art that hemopoietin factors (also known as cytokines) are "involved in systemic humoral regulation of hemopoietic or immune functions." See, e.g., the specification, at the paragraph bridging pages 1 and 2. In view of this knowledge, "a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process)." Also, for the remarks set forth above in Part I, a person of ordinary skill in the art would appreciate that the utilities of the invention are "specific, substantial, and credible." Accordingly, the nucleic acids of claim 1 possess well-established utilities.

Claim 2 is drawn to an isolated nucleic acid containing a sequence encoding NR10.1, NR10.2, or NR10.3, or a fragment thereof. Claim 20 is drawn to an isolated nucleic acid containing a coding region of any one of SEQ ID NOs:1, 3, and 16, the nucleotide sequences corresponding to NR10.1, NR10.2, and NR10.3, respectively. Claim 24 covers an isolated

nucleic acid comprising a nucleotide sequence encoding a protein that comprises the amino acid sequence of any one of SEQ ID NOs:2, 4, and 17, with a single amino acid replacement, deletion, insertion, or addition, where the protein binds to a hematopoietin factor. For the same reasons as discussed above for claim 1, these claims also meet the utility requirement. So do claims 3-8, 21-23, and 25-27, which are drawn to vectors or transformants containing the nucleic acid of claim 1, 2, 20, or 24.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejected claims 1-8 for lack of enablement, contending that these claims do not meet the utility requirement so one of skill in the art would not know how to use the claimed invention. See page 4, lines 9-12 of the Office Action. As set forth above, all of the claimed invention do possess utilities. Thus, withdrawal of the enablement rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected claims 1, 3, 5, and 7 for not complying with the written description requirement. More specifically, he stated that "[c]laim 1(c) is drawn to a nucleic acid that encodes a modified protein that is functionally equivalent [to] NR10 ... As there is no data regarding a function for ... NR10, one would not be able to determine if the modified protein retained that function." See the Office Action, page 4, lines 17-21.

Applicants have deleted claim 1(c) and added new claim 24. This new claim recites a specific function of NR10. It is therefore submitted that the rejection should be withdrawn.

CONCLUSION

Applicants submit that claims 1-8 and 20-27 are in condition for allowance, and such action is respectfully requested.

Enclosed is a check for $800 for excess claim fees and a $1020 check for the Petition for Extension of Time fee.

Please apply any other charges to deposit account 06-1050, referencing attorney docket 14875-096001.

Respectfully submitted,

Date: 9-14-2005

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Amendments to the Drawings:

The attached replacement sheets of drawings include changes to Figures 1-7, 13, and 14 and replace the original sheets including Figures 1-7, 13, and 14. Applicants have amended the drawings, which show a number of sequences, to include SEQ ID NOs.

Attachments following the last page of this Amendment:

Replacement Sheets (9 pages)

Annotated Sheets Showing Changes (9 pages)

```
LOCUS       AY499342                2903 bp    mRNA    linear   PRI 10-JUL-2004
DEFINITION  Homo sapiens interleukin 31RA splice variant x4 (IL31RA) mRNA,
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ACCESSION   AY499342
VERSION     AY499342.1  GI:46276462
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
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            Hominidae; Homo.
REFERENCE   1  (bases 1 to 2903)
  AUTHORS   Dillon,S.R., Sprecher,C., Hammond,A., Bilsborough,J.,
            Rosenfeld-Franklin,M., Presnell,S.R., Haugen,H.S., Maurer,M.,
            Harder,B., Johnston,J., Bort,S., Mudri,S., Kuijper,J.L.,
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            Lockwood,L., Levin,S.D., LeCiel,C., Waggie,K., Day,H., Topouzis,S.,
            Kramer,J., Kuestner,R., Chen,Z., Foster,D., Parrish-Novak,J. and
            Gross,J.A.
  TITLE     Interleukin 31, a cytokine produced by activated T cells, induces
            dermatitis in mice
  JOURNAL   Nat. Immunol. 5 (7), 752-760 (2004)
   PUBMED   15184896
REFERENCE   2  (bases 1 to 2903)
  AUTHORS   Dillon,S.R., Sprecher,C., Hammond,A., Rosenfeld-Franklin,M.,
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            Johnston,J., Bort,S., Mudri,S., Kuijper,J., Bukowski,T., Shea,P.,
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  TITLE     Direct Submission
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ORIGIN

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query.aln
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IL-31RAV4       SI
seq17           SI
                **


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 CLUSTAL W (1.83) Multiple Sequence Alignments



Sequence format is Clustal
Sequence 1: IL-31RA         662 aa
Sequence 2: seq17           662 aa
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ACCESSION   NM_139017
VERSION     NM_139017.3  GI:38455420
KEYWORDS    .
SOURCE      Homo sapiens (human)
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REFERENCE   1  (bases 1 to 2315)
  AUTHORS   Dreuw,A., Radtke,S., Pflanz,S., Lippok,B.E., Heinrich,P.C. and
            Hermanns,H.M.
  TITLE     Characterization of the signaling capacities of the novel
            gp130-like cytokine receptor
  JOURNAL   J. Biol. Chem. 279 (34), 36112-36120 (2004)
   PUBMED   15194700
  REMARK    GeneRIF: the molecular mechanisms underlying GPL-mediated signal
            transduction
REFERENCE   2  (bases 1 to 2315)
  AUTHORS   Dillon,S.R., Sprecher,C., Hammond,A., Bilsborough,J.,
            Rosenfeld-Franklin,M., Presnell,S.R., Haugen,H.S., Maurer,M.,
            Harder,B., Johnston,J., Bort,S., Mudri,S., Kuijper,J.L.,
            Bukowski,T., Shea,P., Dong,D.L., Dasovich,M., Grant,F.J.,
            Lockwood,L., Levin,S.D., LeCiel,C., Waggie,K., Day,H., Topouzis,S.,
            Kramer,J., Kuestner,R., Chen,Z., Foster,D., Parrish-Novak,J. and
            Gross,J.A.
  TITLE     Interleukin 31, a cytokine produced by activated T cells, induces
            dermatitis in mice
  JOURNAL   Nat. Immunol. 5 (7), 752-760 (2004)
   PUBMED   15184896
REFERENCE   3  (bases 1 to 2315)
  AUTHORS   Diveu,C., Lelievre,E., Perret,D., Lak-Hal,A.H., Froger,J.,
            Guillet,C., Chevalier,S., Rousseau,F., Wesa,A., Preisser,L.,
            Chabbert,M., Gauchat,J.F., Galy,A., Gascan,H. and Morel,A.
  TITLE     GPL, a novel cytokine receptor related to GP130 and leukemia
            inhibitory factor receptor
  JOURNAL   J. Biol. Chem. 278 (50), 49850-49859 (2003)
   PUBMED   14504285
  REMARK    GeneRIF: GPL is a novel cytokine receptor related to GP130 and
            leukemia inhibitory factor receptor
REFERENCE   4  (bases 1 to 2315)
  AUTHORS   Clark,H.F., Gurney,A.L., Abaya,E., Baker,K., Baldwin,D., Brush,J.,
            Chen,J., Chow,B., Chui,C., Crowley,C., Currell,B., Deuel,B.,
            Dowd,P., Eaton,D., Foster,J., Grimaldi,C., Gu,Q., Hass,P.E.,
            Heldens,S., Huang,A., Kim,H.S., Klimowski,L., Jin,Y., Johnson,S.,
            Lee,J., Lewis,L., Liao,D., Mark,M., Robbie,E., Sanchez,C.,
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            Schoenfeld,J., Seshagiri,S., Simmons,L., Singh,J., Smith,V.,
            Stinson,J., Vagts,A., Vandlen,R., Watanabe,C., Wieand,D., Woods,K.,
            Xie,M.H., Yansura,D., Yi,S., Yu,G., Yuan,J., Zhang,M., Zhang,Z.,
            Goddard,A., Wood,W.I., Godowski,P. and Gray,A.
  TITLE     The secreted protein discovery initiative (SPDI), a large-scale
            effort to identify novel human secreted and transmembrane proteins:
            a bioinformatics assessment
  JOURNAL   Genome Res. 13 (10), 2265-2270 (2003)
   PUBMED   12975309
REFERENCE   5  (bases 1 to 2315)
  AUTHORS   Ghilardi,N., Li,J., Hongo,J.A., Yi,S., Gurney,A. and de
            Sauvage,F.J.
  TITLE     A novel type I cytokine receptor is expressed on monocytes, signals
            proliferation, and activates STAT-3 and STAT-5
  JOURNAL   J. Biol. Chem. 277 (19), 16831-16836 (2002)
   PUBMED   11877449
  REMARK    GeneRIF: A novel type I cytokine receptor is expressed on
            monocytes, signals proliferation, and activates STAT-3 and STAT-5.
COMMENT     VALIDATED REFSEQ: This record has undergone preliminary review of
            the sequence, but has not yet been subject to final review. The
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            On Nov 20, 2003 this sequence version replaced gi:21314784.
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                     go_function: cytokine binding [goid 0019955] [evidence
                     NAS] [pmid 11877449];
                     go_function: protein kinase binding [goid 0019901]
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                     go_function: transcription coactivator activity [goid
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                     go_function: hematopoietin/interferon-class (D200-domain)
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                     go_process: negative regulation of macrophage activation
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Figure 1

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Figure 2

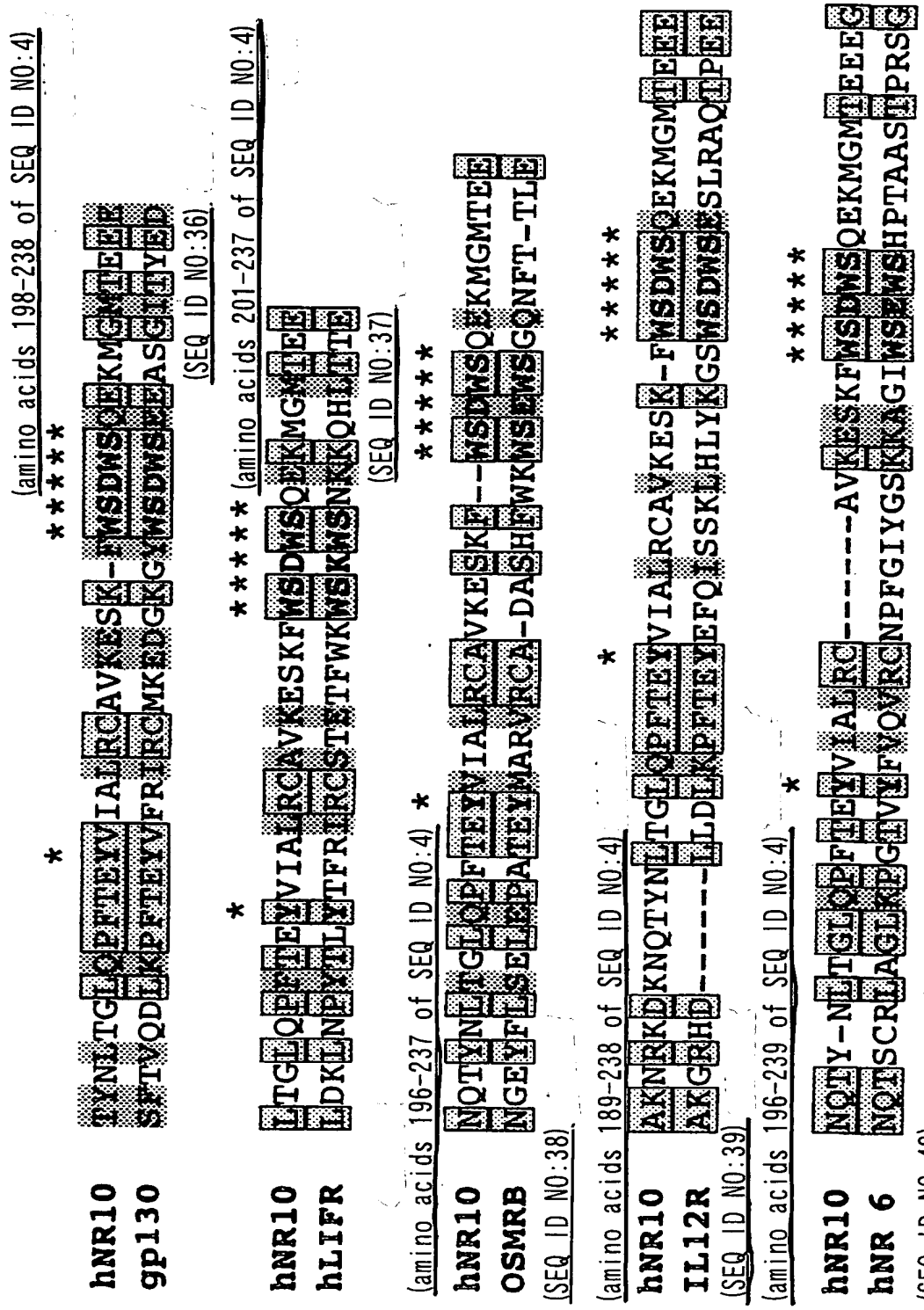

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Figure 3

(SEQ ID NO:1)

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 241 TTTTTCACCACGGCATGTGTCTGTGAATGTCCGCAAAACATTTTAACAATAATGCAATCC
 301 ATTTCCCAGCATAAGTGGGTAAGTGCCACTTTGACTTGGGCTGGGCTTAAAAGCACAAGA
 361 AAAGCTCGCAGACAATCAGAGTGGAAACACTCCCACATCTTAGTGTGGATAAATTAAAGT
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(SEQ ID NO:2) MetLysLeuSerProGln

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Figure 4

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Figure 5

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2281  AAGGATAAGCTAAACCTGAAGGAGTCTGATGACTCTGTGAACACAGAAGACAGGATCTTA
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2461  AGGGGAAAAGAATGGGACTAGAATTCTGTCTTCCTGCCCAACTTCAATATAAGTGTGGAC
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2521  TAAAATGCGAGAAAGGTGTCCTGTGGTCTATGCAAATTAGAAAGGACATGCAGAGTTTTC
2581  CAACTAGGAAGACTGAATCTGTGGCCCCAAGAGAACCATCTCCGAAGACTGGGTATGTGG
2641  TCTTTTCCACACATGGACCACCTACGGATGCAATCTGTAATGCATGTGCATGAGAAGTCT
2701  GTTATTAAGTAGAGTGTGAAAACATGGTTATGGTAATAGGAACAGCTTTTAAAATGCTTT
2761  TGTATTTGGGCCTTTCACACAAAAAAGCCATAATACCATTTTCATGTAATGCTATACTTC
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2941  AAAAAAAAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:1)
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Figure 6

(SEQ ID NO:3)

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(SEQ ID NO:4) MetLysLeuSerProGln

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     LeuGlyIleLysArgMetIleGlnIleGluTrpIleLysProGluLeuAlaProValSer
1021 TCTGATTTAAAATACACACTTCGATTCAGGACAGTCAACAGTACCAGCTGGATGGAAGTC
     SerAspLeuLysTyrThrLeuArgPheArgThrValAsnSerThrSerTrpMetGluVal
1081 AACTTCGCTAAGAACCGTAAGGATAAAAACCAAACGTACAACCTCACGGGGCTGCAGCCT
     AsnPheAlaLysAsnArgLysAspLysAsnGlnThrTyrAsnLeuThrGlyLeuGlnPro
1141 TTTACAGAATATGTCATAGCTCTGCGATGTGCGGTCAAGGAGTCAAAGTTCTGGAGTGAC
     PheThrGluTyrValIleAlaLeuArgCysAlaValLysGluSerLysPheTrpSerAsp
```

Figure 7

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1201  TGGAGCCAAGAAAAAATGGGAATGACTGAGGAAGAAGGCAAGCTACTCCCTGCGATTCCC
      TrpSerGlnGluLysMetGlyMetThrGluGluGluGlyLysLeuLeuProAlaIlePro
1261  GTCCTGTCTACTCTGGTGTAGGGCTGCTTTGGGCTAGACTTGGTGGGGTTTGTCACCACC
      ValLeuSerThrLeuVal***  (SEQ ID NO:4)
1321  TGGTTGGGAATCATGGAATCTCATGACCCCAGGGGCCCCCTGTACCATCGAGAGTGAGCC
1381  TGCACAACTTTGTGCCCCAAAGGCAAAGGATCACATTTTAATACTCATGAGGTTCTTATA
1441  CTATACATGAAAGGGTATCATATCATTTGTTTTGTTTTGTTTTGTTTTTGAGATGGAGTC
1501  TTACTCTGTCACCCAGGATGGAGTGCAGTGATGTGATCTCGGCTCACTGCCACCACCACC
1561  TCCCGAGTTCAAGCAATTCTTGTGCCTCAGCCTCCCAAGTAGCTGGGATTACAGGGGCCC
1621  ACGACCATGCCCGGTTGATTTTTGTATTTTTAGTAGAGAAGGGATATCACCATGTTGGCT
1681  AGGCTAGTCTTGAACTCCTGACCTCAGGTAATCTGCCCACCTTGACCTCCCAAAGTGTTG
1741  GGATTACAGGCGTGAGCCACTGTGCCCCGCCAGTATCATATCATCTGAAGGTATCCTGTG
1801  ATAAATTAAAGATACATATTGTGAATCCTGGAGCTACTACTCAAAAAATAAATAAAGGTG
1861  TAACTAATACAATTTAAAAAATCACATTTTTAATGACAGTGAGGAAAGGAAAGAGGCATG
1921  GATTGCAGGTTGATGGAGTGCTTACTAAGTGTCAGTATGGTCATTAAGAGCAACGCTTCC
1981  AGTCAGTGGCCTTGGCTTAAATCCCAAGCCAGGTGTCTTTGGGCAAGATACCTAAACTCT
2041  CAGTTCATTCTCAGCAGTTTCCTCGCATTTATTCCCCTTTTCTATATTGAAATAGAATAT
2101  GTAAGTTGAGTTTATAGTAGTACCTATTTTTTAGTATTATTTTAAAGATTAAATGAAATA
2161  ATGTGTTTAGCCCATAGTAGATATTCACTAACTGCTAGACTTCCTATTCTTATTATTTAT
2221  CCTCCTACTATTATTTTTAATCCTCCTTAAAGCACTATAAAATATGTAGAGTCACTCCCA
2281  TTTTGGAAATGAGGAAACTGAGTTTCAGAGATGCTAATAAACAGCTCAGGGTCACTCAGC
2341  ATGTGTTACTTTTCTCAAGAGCCTTGCCCAGAGTCTGACCCTCAGTGGACGATCAATAAA
2401  TGTGTGATGAATGGAAAAAAAAAAAAAAAAAAAAAAAAA  (SEQ ID NO:3)
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Figure 13

(SEQ ID NO:16)

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   1 CCCCTGATACATGAAGCTCTCTCCCCAGCCTTCATGTGTTAACCTGGGGATGATGTGGAC
(SEQ ID NO:17)  MetLysLeuSerProGlnProSerCysValAsnLeuGlyMetMetTrpThr
  61 CTGGGCACTGTGGATGCTCCCCTCACTCTGCAAATTCAGCCTGGCAGCTCTGCCAGCTAA
     TrpAlaLeuTrpMetLeuProSerLeuCysLysPheSerLeuAlaAlaLeuProAlaLys
 121 GCCTGAGAACATTTCCTGTGTCTACTACTATAGGAAAAATTTAACCTGCACTTGGAGTCC
     ProGluAsnIleSerCysValTyrTyrTyrArgLysAsnLeuThrCysThrTrpSerPro
 181 AGGAAAGGAAACCAGTTATACCCAGTACACAGTTAAGAGAACTTACGCTTTTGGAGAAAA
     GlyLysGluThrSerTyrThrGlnTyrThrValLysArgThrTyrAlaPheGlyGluLys
 241 ACATGATAATTGTACAACCAATAGTTCTACAAGTGAAAATCGTGCTTCGTGCTCTTTTTT
     HisAspAsnCysThrThrAsnSerSerThrSerGluAsnArgAlaSerCysSerPhePhe
 301 CCTTCCAAGAATAACGATCCCAGATAATTATACCATTGAGGTGGAAGCTGAAAATGGAGA
     LeuProArgIleThrIleProAspAsnTyrThrIleGluValGluAlaGluAsnGlyAsp
 361 TGGTGTAATTAAATCTCATATGACATACTGGAGATTAGAGAACATAGCGAAAACTGAACC
     GlyValIleLysSerHisMetThrTyrTrpArgLeuGluAsnIleAlaLysThrGluPro
 421 ACCTAAGATTTTCCGTGTGAAACCAGTTTTGGGCATCAAACGAATGATTCAAATTGAATG
     ProLysIlePheArgValLysProValLeuGlyIleLysArgMetIleGlnIleGluTrp
 481 GATAAAGCCTGAGTTGGCGCCTGTTTCATCTGATTTAAAATACACACTTCGATTCAGGAC
     IleLysProGluLeuAlaProValSerSerAspLeuLysTyrThrLeuArgPheArgThr
 541 AGTCAACAGTACCAGCTGGATGGAAGTCAACTTCGCTAAGAACCGTAAGGATAAAAACCA
     ValAsnSerThrSerTrpMetGluValAsnPheAlaLysAsnArgLysAspLysAsnGln
 601 AACGTACAACCTCACGGGGCTGCAGCCTTTTACAGAATATGTCATAGCTCTGCGATGTGC
     ThrTyrAsnLeuThrGlyLeuGlnProPheThrGluTyrValIleAlaLeuArgCysAla
 661 GGTCAAGGAGTCAAAGTTCTGGAGTGACTGGAGCCAAGAAAAAATGGGAATGACTGAGGA
     ValLysGluSerLysPheTrpSerAspTrpSerGlnGluLysMetGlyMetThrGluGlu
 721 AGAAGCTCCATGTGGCCTGGAACTGTGGAGAGTCCTGAAACCAGCTGAGGCGGATGGAAG
     GluAlaProCysGlyLeuGluLeuTrpArgValLeuLysProAlaGluAlaAspGlyArg
 781 AAGGCCAGTGCGGTTGTTATGGAAGAAGGCAAGAGGAGCCCCAGTCCTAGAGAAAACACT
     ArgProValArgLeuLeuTrpLysLysAlaArgGlyAlaProValLeuGluLysThrLeu
 841 TGGCTACAACATATGGTACTATCCAGAAAGCAACACTAACCTCACAGAAACAATGAACAC
     GlyTyrAsnIleTrpTyrTyrProGluSerAsnThrAsnLeuThrGluThrMetAsnThr
 901 TACTAACCAGCAGCTTGAACTGCATCTGGGAGGCGAGAGCTTTTGGGTGTCTATGATTTC
     ThrAsnGlnGlnLeuGluLeuHisLeuGlyGlyGluSerPheTrpValSerMetIleSer
 961 TTATAATTCTCTTGGGAAGTCTCCAGTGGCCACCCTGAGGATTCCAGCTATTCAAGAAAA
     TyrAsnSerLeuGlyLysSerProValAlaThrLeuArgIleProAlaIleGlnGluLys
1021 ATCATTTCAGTGCATTGAGGTCATGCAGGCCTGCGTTGCTGAGGACCAGCTAGTGGTGAA
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Figure 14

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        SerPheGlnCysIleGluValMetGlnAlaCysValAlaGluAspGlnLeuValValLys
1081    GTGGCAAAGCTCTGCTCTAGACGTGAACACTTGGATGATTGAATGGTTTCCGGATGTGGA
        TrpGlnSerSerAlaLeuAspValAsnThrTrpMetIleGluTrpPheProAspValAsp
1141    CTCAGAGCCCACCACCCTTTCCTGGGAATCTGTGTCTCAGGCCACGAACTGGACGATCCA
        SerGluProThrThrLeuSerTrpGluSerValSerGlnAlaThrAsnTrpThrIleGln
1201    GCAAGATAAATTAAAACCTTTCTGGTGCTATAACATCTCTGTGTATCCAATGTTGCATGA
        GlnAspLysLeuLysProPheTrpCysTyrAsnIleSerValTyrProMetLeuHisAsp
1261    CAAAGTTGGCGAGCCATATTCCATCCAGGCTTATGCCAAAGAAGGCGTTCCATCAGAAGG
        LysValGlyGluProTyrSerIleGlnAlaTyrAlaLysGluGlyValProSerGluGly
1321    TCCTGAGACCAAGGTGGAGAACATTGGCGTGAAGACGGTCACGATCACATGGAAAGAGAT
        ProGluThrLysValGluAsnIleGlyValLysThrValThrIleThrTrpLysGluIle
1381    TCCCAAGAGTGAGAGAAAGGGTATCATCTGCAACTACACCATCTTTTACCAAGCTGAAGG
        ProLysSerGluArgLysGlyIleIleCysAsnTyrThrIlePheTyrGlnAlaGluGly
1441    TGGAAAAGGATTCTCCAAGACAGTCAATTCCAGCATCTTGCAGTACGGCCTGGAGTCCCT
        GlyLysGlyPheSerLysThrValAsnSerSerIleLeuGlnTyrGlyLeuGluSerLeu
1501    GAAACGAAAGACCTCTTACATTGTTCAGGTCATGGCCAGCACCAGTGCTGGGGGAACCAA
        LysArgLysThrSerTyrIleValGlnValMetAlaSerThrSerAlaGlyGlyThrAsn
1561    CGGGACCAGCATAAATTTCAAGACATTGTCATTCAGTGTCTTTGAGATTATCCTCATAAC
        GlyThrSerIleAsnPheLysThrLeuSerPheSerValPheGluIleIleLeuIleThr
1621    TTCTCTGATTGGTGGAGGCCTTCTTATTCTCATTATCCTGACAGTGGCATATGGTCTCAA
        SerLeuIleGlyGlyGlyLeuLeuIleLeuIleIleLeuThrValAlaTyrGlyLeuLys
1681    AAAACCCAACAAATTGACTCATCTGTGTTGGCCCACCGTTCCCAACCCTGCTGAAAGTAG
        LysProAsnLysLeuThrHisLeuCysTrpProThrValProAsnProAlaGluSerSer
1741    TATAGCCACATGGCATGGAGATGATTTCAAGGATAAGCTAAACCTGAAGGAGTCTGATGA
        IleAlaThrTrpHisGlyAspAspPheLysAspLysLeuAsnLeuLysGluSerAspAsp
1801    CTCTGTGAACACAGAAGACAGGATCTTAAAACCATGTTCCACCCCCAGTGACAAGTTGGT
        SerValAsnThrGluAspArgIleLeuLysProCysSerThrProSerAspLysLeuVal
1861    GATTGACAAGTTGGTGGTGAACTTTGGGAATGTTCTGCAAGAAATTTTCACAGATGAAGC
        IleAspLysLeuValValAsnPheGlyAsnValLeuGlnGluIlePheThrAspGluAla
1921    CAGAACGGGTCAGGAAAACAATTTAGGAGGGGAAAAGAATGGGACTAGAATTCTGTCTTC
        ArgThrGlyGlnGluAsnAsnLeuGlyGlyGluLysAsnGlyThrArgIleLeuSerSer
1981    CTGCCCAACTTCAATATAAGTGTGGACTAAAATGCGAGAAAGGTGTCCTGTGGTCTATGC
        CysProThrSerIle*** (SEQ ID NO:17)
2041    AAATTAGAAAGGACATGCAGAGTTTTCCAACTAGGAAGACTGAATCTGTGGCCCCAAGAG

2101    AACCATCTCCGAAGACTGG (SEQ ID NO:16)
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